43. The polynucleotide of claim 3, wherein the Vff2p comprises SEQ ID NO:2.

44. (Amended) The protein of claim 36[25], wherein the yeast is *S. cerevisiae*.

45. The protein of claim 36, wherein the protein is from *S. cerevisiae*.

46. The method of claim 37, wherein the yeast cell is a *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Yarrowia lipolytica*, *Pichia pastoris*, *Hansenula polymorpha*, or *Kluyveromyces lactis* cell.

REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on July 5, 2001, and the references cited therewith.

Claims 3-12, 14-23, 25-27, 29-34, and 36-46 are now pending in this application. Claims 3, 4, 12, 14, 15, 25, 26, 31, 32, 33, 34, 36, 37 and 44 have been amended.

Claim Objection

Claim 12 was objected to as depending from a canceled claim. Claim 12 has been amended to depend from claim 3. Applicants request withdrawal of this objection.

Section 112, First Paragraph, Rejections

The Examiner has made written description and enablement rejections under the first paragraph of 35 U.S.C. § 112. These two rejections are addressed together below.

Claims 3-12, 14-23, 25-27, 29-34, 36-42 and 44-46 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, claims directed to polynucleotides encoding a functional vesicular fusion factor 2 protein (Vff2p) having SEQ ID NO:2 and variant polypeptides thereof do not

have specific limitations and essentially are overly broad, particularly because of the term "variant."

Claims 3-12, 14-23, 25-27, 29-34, 36-42 and 44-46 have also been rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for a polynucleotide with a sequence of SEQ ID NO:1, a protein with a sequence of SEQ ID NO:2, and a host cell (*Saccharomyces cerevisiae*), allegedly does not reasonably provide enablement for polynucleotide and/or protein variants other than SEQ ID NOs:1 and 2 or a host cell other than *Saccharomyces cerevisiae*. According to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants submit that the specification clearly shows that Applicants were in possession of the claimed subject matter at the time of filing and that the claimed invention is enabled and not overly broad. However, to facilitate prosecution of the application, a definition for "variants" has been substituted for this word. Accordingly, the claims are now directed to polynucleotides encoding Vff2 proteins with greater than 36% sequence identity to SEQ ID NO:2. Support for this subject matter can be found in the specification, for example, at page 11, lines 1-11. In some claims the Vff2 polynucleotide is defined as having SEQ ID NO:1 or a sequence encoding SEQ ID NO:2. Support for this subject matter can be found in the specification, for example, at page 4, lines 18-26 and at page 8, lines 17-23. The claims further recite that the Vff2p increases yeast cell growth or protein secretion. Support for this subject matter can be found throughout the specification, for example, in the Examples. Accordingly, no new matter has been added to the claimed subject matter.

Claims 3-12, 14-23, 25-27, 29-30 and 43 are therefore directed to polynucleotides, expression vectors, and yeast host cells that encode a functional vesicular fusion factor 2 protein (Vff2p) with greater than 36% sequence identity with SEQ ID NO:2, wherein the Vff2p increases yeast cell growth or protein secretion. In some claims, the Vff2p polynucleotide comprises SEQ ID NO:1 or a sequence encoding SEQ ID NO:2.

Claim 31-34 are directed to a method for increasing cell growth of a yeast host cell, comprising introducing Vff2p into the cell and culturing the cell, wherein the Vff2p has greater than 36% sequence identity to SEQ ID NO:2.

Claims 37-42 and 46 are directed to a method of selecting for a yeast secretory mutant cell containing a polynucleotide sequence encoding a Vff2p operably linked to a promoter, wherein the Vff2p comprises SEQ ID NO:2, or a Vff2p with greater than 36% identity to SEQ ID NO:2, the method comprising growing the yeast secretory mutant cell at a restrictive temperature of about 32-37°C, wherein the restrictive temperature selectively favors mutant cell growth.

Written Description

The Examiner has stated that the first rejection under section 112 is based on the "Written Description" requirement published in the Federal Register (Volume 64, Number 244, Pages 71427-71440). Applicants note that the Guidelines in this publication are superceded by the January 5, 2001 publication of "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, P1, 'Written Description' Requirement," 66 Fed. Reg. 1099, 1099 (Jan. 5, 2001)("New Guidelines"). These New Guidelines state as follows:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

66 Fed. Reg. at 1104. The New Guidelines also provide guidance as to how the written description requirement can be satisfied.

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

Id.

Applicants submit that the claims describe the claimed invention with all of its limitations using such descriptive means as words, structures, and formulas that fully set forth the claimed invention. In particular, the claims identify specific sequences Vff2p and a specific degree of sequence identity that distinctly determine the structural boundaries of the invention. Moreover, the claims also require that the encoded Vff2p increase yeast cell growth or protein secretion, thereby specifying the functional boundaries of the invention.

Applicants have shown that they were in possession of the invention at the time of filing by describing an actual reduction to practice. In particular, applicants describe the cloning of Vff2p, its sequence and its function -- increasing secretion and cell growth. *See* Sequence Listing, Examples 1-3 and Figures 1-3. Applicants have therefore described the distinguishing and identifying characteristics of the invention in a manner sufficient to show that the inventors were in possession of the claimed invention.

Moreover, contrary to the Examiner's allegations, Applicants need not describe every nuance of the invention in order to satisfy the written description requirement.

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

New Guidelines at 1106. Accordingly, Applicants have provided a description showing that the inventors were in possession of the invention and respectfully request withdrawal of this written description rejection under 35 U.S.C. § 112, first paragraph.

Enablement

The Examiner has raised enablement issues by analyzing the factors described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) in relation to the first rejection. In the second rejection, the Examiner has alleged that the specification lacks enablement for host cells other than *Saccharomyces cerevisiae* and for Vff2 polynucleotides and proteins other than SEQ ID NO:1 and 2, respectively .

In the analysis of *Wands* factors, the Examiner has stated that the claims are broad in that they encompass both the Vff2 protein from *Saccharomyces cerevisiae* and any protein and/or nucleic acid sequence from any other organism or altered version of the *Saccharomyces*

cerevisiae sequence that is not completely identical to the native Vff2 protein. *See* Official Action at 5 (Jul. 5, 2001). The Examiner has also alleged that the working examples only relate to SEQ ID NOs:1 and 2 wherein the host cell is *Saccharomyces cerevisiae*. *See* Official Action at 6 (Jul. 5, 2001). Furthermore, while the Examiner concedes that the skill in the art is high, she alleges the area of the invention is unpredictable. *See* Official Action at 5 (Jul. 5, 2001).

Applicants submit that the claims of the application recite a specific functions and defined structures. In particular, the claims are directed to functional Vff2 polynucleotides and proteins with clearly defined structural limitations. Moreover, the claims further specify that the functions of the Vff2 polynucleotides and proteins are those that are uniquely described and provided within the specification (increasing yeast cell growth and/or protein secretion). Furthermore, the claimed host cells are defined as yeast cells (*see, e.g.*, claim 25).

Applicants also submit that the area of the invention is not so unpredictable as the Examiner has alleged. As admitted by the Examiner, the level of skill in the art is high. A skilled artisan need only apply routine sequencing and sequence comparison procedures to identify polynucleotides and proteins having the claimed percent and/or position of sequence changes. In particular, the specification discloses SEQ ID NO:1 and SEQ ID NO:2 as well as methods for identifying related polynucleotides, for example, by doing a BLAST analysis (*see, e.g.*, page 11, lines 3-11) or by performing the screening procedures provided in the Examples. To determine whether the polynucleotides and polypeptides function in the claimed manner, a skilled artisan can perform any of the tests and procedures described in the specification, for example, transformation of a yeast host cell with a selected Vff2 polynucleotide and observation of whether a functional Vff2 polypeptide is produced by assessing the rate of secretion and cell growth of that host cell (*see, e.g.*, Example 3). One of skill in the art understands that the claimed Vff2 proteins can function in any yeast species, because the cellular structures and life cycles of yeast species are similar. If any ambiguity or variation in function were observed from one yeast species to another, one of skill in the art can adapt the inventive polynucleotide and proteins using the teachings of the specification, so that they can be used a variety of yeast host cells. Hence, by use of a combination of routine procedures and the teachings of the

specification, one of skill in the art can clearly establish which proteins, polynucleotides and recombinant host cells have the claimed features, and which do not.

The Federal Circuit has explicitly recognized that a need to carry out extensive synthesis and screening programs to locate bioactive molecules does not constitute undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1406-1407 (Fed. Cir. 1988). In *Wands,* the court held that a process of immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics did not require undue experimentation. The Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Id. The nature of genetic and molecular biological research involves screening the sequences of nucleic acids and determining the functions of encoded proteins. Practitioners in this art are readily prepared to screen negative sequences in order to find one that makes the desired protein.

Moreover, the fact that a claim may encompass a large number of Vff2p polynucleotides or polypeptides or host cells is not dispositive of the enablement issue. This is particularly true in an art area in which the level of skill is very high. Practitioners in the art related to the present application are well-equipped to locate and test additional Vff2p-encoding polynucleotides in various host cells for polypeptides with the claimed activities. *See also, Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics were available to art convincing of enablement).

Accordingly, a skilled artisan would have understood that the inventors were in possession of the invention at the time of filing and that the specification enabled such a skilled artisan to make and use the full scope of the invention. Applicants respectfully request withdrawal of the written description and enablement rejections made under 35 U.S.C. § 112, first paragraph.

§112 Second Paragraph Rejections

Claims 31-34 and 44 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has alleged that claim 31 is incomplete because the process step(s) do not refer back to the method recited in the preamble. Applicants submit that 35 USC § 112, second paragraph, does not require that the preamble be referenced within the steps of a method claim. Instead, 35 USC § 112, second paragraph, has only two requirements: (A) the claims must set forth the subject matter that applicants regard as their invention; and (b) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Applicants submit that each and every step required to practice the method of claim 31 is recited therein. One of skill would readily understand the language of claim 31, particularly in light of the teachings of Example 3 and Figures 3A and 3B showing that the only steps required for increasing cell growth of a host cell are introducing Vff2p into the cell and culturing the cell. Accordingly, the language of claim 31 is clear and definite and reference back to the preamble is unnecessary. Applicants respectfully request withdrawal of this rejection of claim 31 under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 31 and 33 as allegedly indefinite for reciting "has at least 40% homology to SEQ ID NO:2." Applicants submit that the claims are clear and definite and that the meaning of this term is clear, particularly in light of the teachings of the specification at page 11, lines 6-11. However, to facilitate prosecution of the application, applicants have replaced "at least 40% homology" with "greater than 36% sequence identity." Support for this terminology can be found in the specification, for example, at page 11, lines 6-11. Applicants respectfully request withdrawal of this rejection of claims 31and 33 under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 32 and 34 as the term "the encoded Vff2p" allegedly has insufficient antecedant basis. Applicants submit that the claims are clear and definite and that the meaning of this term is clear, however, to facilitate prosecution of the application, applicants have deleted the word "encoded" from claims 32 and 34. Applicants respectfully

request withdrawal of this rejection of claims 32 and 34 under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 44 as allegedly indefinite for reciting "the protein of claim 25" while claim 25 refers to a recombinant host cell. Applicants submit that this inadvertent typographical error has been corrected by substitution of "36" for "25." Applicants respectfully request withdrawal of this rejection of claim 44 under 35 U.S.C. § 112, second paragraph.

§102 Rejection of the Claims

Claims 3-12, 14-23, 25-27, 29-34 and 36-46 were rejected under 35 USC § 102(a) as allegedly anticipated by Powell et al. (Mol. Biol. Cell 10(suppl):298a, abstract No. 1727, November 1999, IDS reference). According to the Examiner, Powell et al. disclose a 32 kilodalton vesicle fusion factor 2 protein that is involved in membrane fusion, and the Examiner asserts that this protein appears to be the same protein or a variant thereof that is claimed in the instant invention.

Applicants submit that this rejection must be withdrawn because the Powell et al. abstract fails to disclose each and every element of claims 3-12, 14-23, 25-27, 29-34 and 36-46, as required by 35 USC § 102(a). The standard for anticipation is one of strict identity, and to anticipate a claim for a patent a single prior art source must contain all its elements. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q.2d 90 (Fed. Cir. 1986); In re Dillon, 16 U.S.P.Q.2d 1987 (Fed. Cir. 1990). Furthermore, there must be no difference between the claimed invention and the disclosure, as viewed by a person of ordinary skill in the art. Scripps Clinic & Res. Found. v. Genentech, Inc., 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

Claims 3-12, 14-23, 25-27, 29-30 and 43 are directed to polynucleotides, expression vectors, and yeast host cells that encode a functional vesicular fusion factor 2 protein (Vff2p) with greater than 36% sequence identity with SEQ ID NO:2, wherein the Vff2p increases yeast cell growth or protein secretion. In some claims, the Vff2p polynucleotide comprises SEQ ID NO:1 or a sequence encoding SEQ ID NO:2.

Claim 31-34 are directed to a method for increasing cell growth of a yeast host cell, comprising introducing Vff2p into the cell and culturing the cell, wherein the Vff2p has greater than 36% sequence identity to SEQ ID NO:2.

Claims 37-42 and 46 are directed to a method of selecting for a yeast secretory mutant cell containing a polynucleotide sequence encoding a Vff2p operably linked to a promoter, wherein the Vff2p comprises SEQ ID NO:2, or a Vff2p with greater than 36% identity to SEQ ID NO:2, the method comprising growing the yeast secretory mutant cell at a restrictive temperature of about 32-37°C, wherein the restrictive temperature selectively favors mutant cell growth.

These claims are not anticipated by Powell et al. because this abstract does not disclose a nucleotide or amino acid sequence for any vesicle fusion factor 2 protein. Nor does Powell et al. disclose a protein, much less a vesicle fusion factor 2 protein, that can increase cell growth. Similarly, Powell et al. does not disclose a method for increasing cell growth or for increasing protein secretion of a host cell by introducing Vff2p into the cell and culturing the cell, because Powell et al. does not disclose what polynucleotide or amino acid sequence should be used to introduce Vff2p into a cell. Accordingly, anticipation cannot be found because Powell et al. do not disclose each and every element of the rejected claims.

Moreover, the Powell et al. abstract would not enable one of skill in the art to make and use the claimed subject matter, including the Vff2p protein or a polynucleotide that encodes a Vff2p with the claimed sequences, this abstract does not provide sufficient information on how to locate and identify such a Vff2p protein or polynucleotide. Even if one of skill in the art were to follow the sketchy screening methods provided by Powell et al., the skilled artisan would not know how to find a Vff2p protein or polynucleotide after performing the screen. Clones isolated in such a screen could not be tested to see whether or not they encoded the requisite amino acid sequence or even whether they had homology to the claimed polynucleotide or amino acid sequences. As admitted by the Examiner, "[a]n analysis of the prior art indicates that at the time that the invention was made one of skill in the art did not know how to make and/or use a Vff2 protein." Official Action at 5 (Jul. 5, 2001).

Applicants respectfully request withdrawal of this rejection under 35 USC § 102(a).

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 5th day of November, 2001.

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Name

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Signature